

# The Relationship Between Neutrophil-Lymphocyte Ratio and Empirical Antibiotic Therapy in Patients with Fever of Unknown Origin

Nedeni Bilinmeyen Ateşli Hastalarda Nötrofil-Lenfosit Oranı ile Ampirik Antibiyotik Tedavisi Arasındaki İlişki

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## Abstract

Objective	Empirical antibiotic therapy is usually applied by physicians to patients with fever when the origin of the infection can not yet be determined. The aim of this study is to determine the cost-effectiveness of inflammatory parameters in empirical antibiotic therapy in patients with fever of unknown origin (FUO).
Materials and Methods	A total of 577 patients, whose blood cultures were taken and followed up by the NBA, were divided into two groups as fever group due to infection (IRFG) and fever group not related to infection (NIRFG), and their five-year data were analyzed retrospectively from the patient information registry system. From the complete blood count test results, the neutrophil count was proportioned to the lymphocyte count parameter, and the neutrophil lymphocyte ratio and thrombocyte lymphocyte ratio values were calculated.
Results	Total of 577 patients were divided into two groups as infection related fever group (IRFG) and non-infection related fever group (NIRFG), and were included in the study. The durations of first antibiotic usages were $4.54 \pm 3.08$ (1-14) days and $5.35 \pm 3.8$ (1-21) days in IRFG and NIRFG, respectively. Neutrophil-to-lymphocyte ratio (NLR) was 8.00 (3.00-15.00) in the IRFG, whereas it was 5.00 (3.00-9) in the NIRFG ( $p = 0.001$ ). Platelet-to-lymphocyte ratio (PLR) was 21.00 (9.00-41.00) in the IRFG, whereas it was 16.00 (7.25-27.75) in the NIRFG and was not significant ( $p = 0.165$ ).
Conclusion	Since neutrophil-lymphocyte ratio can be checked from routine blood tests and is not an expensive method, it can be used as an advantageous diagnostic method in patients with fever of unknown origin (FUO).
Keywords	Empirical antibiotic therapy; Fever of unknown origin; Neutrophil to lymphocyte ratio; Platelet-to-lymphocyte ratio.

## Öz

Amaç	Ampirik antibiyotik tedavisi, enfeksiyon kaynağının henüz belirlenemediği durumlarda hekimlerin ateşi olan hastalara yaygın olarak uyguladıkları bir yöntemdir. Bu çalışmanın amacı, nedeni bilinmeyen ateşi olan hastalarda (NBA) ampirik antibiyotik tedavisinde maliyet-etkinin flamatuar parametreleri belirlemektir.
Gereç ve Yöntemler	Kan kültürleri alınmış olan NBA ile takip edilen toplam 577 hasta enfeksiyona bağlı ateş grubu (EBAG, n:203) ve enfeksiyona bağlı olmayan ateş grubu (EBOAG, n:374) olarak iki gruba ayrıldı ve beş yıllık verileri hasta bilgi kayıt sisteminden geriye dönük olarak incelendi. Tam kan test sonuçlarından nötrofil sayısı, lenfosit sayısı parametresine oranlanan nötrofil lenfosit oranı ve trombosit lenfosit oranı değerleri hesaplandı.
Bulgular	Toplam 577 hasta enfeksiyona bağlı ateş grubu (EBAG) ve enfeksiyona bağlı olmayan ateş grubu (EBOAG) olarak iki gruba ayrıldı. İlk antibiyotik kullanım süreleri EBAG ve EBOAG'da sırasıyla $4.54 \pm 3.08$ (1-14) gün ve $5.35 \pm 3.8$ (1-21) gündü ( $p = 0.023$ ). Nötrofil-lenfosit oranı (NLO) EBAG'da 8.00 (3.00-15.00) iken, EBOAG'da 5.00 (3.00-9.00) idi ( $p = 0.001$ ). Trombosit-lenfosit oranı (TLO) EBAG'da 21.00 (9.00-41.00) iken, EBOAG'da 16.00 (7.25-27.75) idi ve anlamlı değildi ( $p = 0.165$ ).
Sonuç	Nötrofil lenfosit oranı rutin kan testlerinden bakılabilen ve pahalı bir yöntem olmaması nedeniyle, nedeni belirlenemeyen ateşli (NBA) hastalarda avantajlı bir tanı metodu olarak kullanılabilir.
Anahtar Kelimeler	Ampirik Antibiyotik Tedavisi; Nedeni Bilinmeyen Ateş; Nötrofil Lenfosit Oranı; Trombosit Lenfosit Oranı.

## INTRODUCTION

Fever of unknown origin (FUO) was initially described by Petersdorf and Beason as body temperature above 38.3 °C. It is defined as fever that is not diagnosed despite on week of research on patients who had fever for at least three weeks and were eventually hospitalized.<sup>1</sup> Although laboratory and diagnostic imaging tests contribute to advanced technology, challenges remain for FUO diagnosis and treatment.<sup>2</sup> FUO consists of four general categories: infectious, neoplastic, non-infectious and others.<sup>3</sup> In most previous studies, infections are indicated as the leading causes of FUO, in which abscess, endocarditis, tuberculosis and complicated urinary tract infections are the main ones.<sup>4</sup> Adult-onset Still's disease (AOSD) and systemic lupus erythematosus are the most common reasons in young individuals of the Non-infectious inflammatory disease (NIID) group. Temporal arteritis and polymyalgia rheumatica are mostly defined in the elderly individuals of NIID group.<sup>5</sup>

It is challenging to differentiate infectious fever from non-infectious on, which in turn makes it difficult to decide starting an antibiotic therapy in patients with non-infectious fever. In those cases, C-reactive protein (CRP) and procalcitonin(PCT) are important biomarkers to conclude whether an empirical antibiotic therapy should be initiated.<sup>6</sup> Also, it has been suggested that the neutrophil:lymphocyte ratio (NLR) in peripheral blood is useful for distinguishing between types of infection and also useful for predicting the outcome of the infection.<sup>7</sup>

Proper empirical antibiotic treatment reduces mortality, along with the duration of intensive care unit and hospitalization.<sup>8</sup> In some cases, antibiotic usage is not applicable. Unnecessary use of antibiotics should be avoided by considering appropriate antibiotic selection and antibiotic resistance on both patient and cost basis. Empirical antibiotic therapy should not be applied if the fever persists over a long time period. Antibiotic application might mask the disease, delay diagnosis and prevent appropriate treat-

ment. One of the most common mistakes in antimicrobial usage is adding or changing antibiotics, although there is no clear evidence of an infectious disease.<sup>9,10</sup>

In this study, we aimed to investigate the distribution of antibiotic treatments applied to patients with FUO, who were admitted to our clinic due to fever and were hospitalized.

## MATERIAL and METHODS

### Study site and study period

This study was conducted between January 1, 2015 and January 1, 2020 at Sakarya Training and Research Hospital (SUTRH) Internal Medicine Clinic. SUTRH has total of 935 beds, in which 120 of them are in the intensive care unit (ICU). This study was performed in the internal medicine clinic of third step hospital, which has 36 beds. Patients who applied to the hospital with fever and received inpatient treatment at the internal medicine clinic were included in the study. Patients were evaluated in two groups as infection related fever group (IRFG) and non-infection related fever group (NIRFG), based on their fever etiologies.

### Infection Related Fever Group (IRFG)

In this groups, the culture of patients, who applied to the clinic with fever, demonstrated reproduction, which is an indicative of an infectious disease.

### Non-Infection Related Fever Group (NIRFG)

In this groups, the culture results of patients, who had fever and were followed up in the clinic turned out negative. Infections were excluded from the source of fever and this group is designated as non-infectious.

### Inclusion and exclusion criteria

All patients being followed up at least one day at SUTRH Internal Medicine Clinic were included in the study. The study group consisted of patients who were admitted with fever. Patients who were followed up in the clinic for less

than 1 day and whose medical records were missing were excluded from the study. Patients under 17 were not included from the study as well.

### Data collection

The medical records of patients who were hospitalized at SUTRH Internal Medicine Clinic and admitted with fever were investigated retrospectively. The culture information of patients, antibiotics received, number of antibiotics administered, as well as initiation and duration of antibiotic usage were recorded on the patient registration form along with additional information regarding hospitalization.

Patient demographics, as well as PCT, CRP, erythrocyte-sedimentation rate (ESR), alanineaminotransferase (ALT), aspartate aminotransferase (AST), creatinine, thyroid stimulant hormone (TSH), lactatedehydrogenase (LDH), white blood cell (WBC), lymphocytes (Lym), neutrophil (Neu), mean platelet volume (MPV) and platelet levels were recorded.

### Laboratory parameters

Blood samples were obtained in the morning, after eight hours of fasting during diagnosis and follow-up, and were sent to the laboratory immediately to be centrifuged at 2000 rpm for 15 minutes. For biochemical parameters, the samples were placed into a dry tube and investigated using a Beckman Coulter AU680<sup>®</sup> with Beckman Coulter kits. Blood was collected into an EDTA coated tube for hemogram examination using a WIC-LYSE for CELL DYN 3700 Kits on the Abbott Cell-Dyn 3700<sup>®</sup> Device.

ESR was performed using Rapida ESR100<sup>®</sup> in capillary tubes. The CRP parameter was studied with SIEMENS BN II<sup>®</sup> with Cardio Phase CRP WN<sup>®</sup> kits. Blood samples for PCT were obtained from the tubes with decomposed serum. PCT was measured with a timely-mannered reinforced cryptate emission technology by measuring the signal sent by time lagged immunocomplex (BIOMERIEUX/mini IDAS). TSH parameter was studied with Abbott Ar-

chitect I 2000 SR<sup>®</sup>. The data was automatically uploaded to the hospital database system and screened consequently. MPV (N: 7.5- 11.5 femtoliter) values were recorded from the measured value in the hemogram.

### Statistical Analysis

Data analysis was performed using IBM SPSS 21 (IBM Corp., Armonk, NY, USA<sup>®</sup>Z). All results are presented as frequencies, percentages, mean  $\pm$  S.D and median [IQR]. Chi-square test was used to compare categorical variables. Kolmogorov-Smirnov test was used to determine whether continuous data were normally distributed. All normally distributed data were analyzed using Student's t-test, while non-normally distributed data were analyzed using the Mann-Whitney U test. The statistically significant two tailed p-value was considered as  $<0.05$  unless otherwise noted.

### Ethics approval

Ethics approval for this study was obtained from Sakarya University Faculty of Medicine Non-Interventional Ethics Committee (Number: 71522473 / 050.01.04/47).

### RESULTS

Throughout the study period, 203 (36%) of 577 patients, who were followed in the clinic for fever, were considered as IRFG and 374 (64%) were NIRFG. In the IRFG, 133 (65.5%) of patients were male, and the mean age was  $66.42 \pm 16.58$  years. Total of 206 (55.1%) patients in the NIRFG were male, and the mean age was  $65.41 \pm 18.03$  years. There was no significant difference between ages ( $p > 0.05$ ). The length of hospitalization was similar in both groups, in which the average length of stay in NIRFG was  $7.97 \pm 6.59$  days and  $8.85 \pm 7.6$  days in IRFG ( $p = 0.145$ , Table 1).

While the mean ESR in IRFG was found  $71.47 \pm 34.28$  mm / h; it was  $62.68 \pm 39.29$  mm / h (N:  $<50$  years;  $<20$  mm/h,  $>50$  years;  $<30$  mm/h) in NIRFG ( $p = 0.013$ ). Mean CRP values were  $141.82 \pm 107.19$  mg / L and  $97.49 \pm 88.77$  mg / L (N: (N:0-5) in IRFG and NIRFG, respectively ( $p = 0.001$ ).

Mean Alb levels were  $2.91 \pm 0.60$  in IRFG and NIFRG was  $3.06 \pm 0.65$  mg/dL (N:3,2-4,6) mg/dL in NIFRG ( $p = 0,006$ ). Median PCT in IRFG was  $1.03(0.22-8.41)$  ng/ml, whereas it was  $0.36(0.09-1.11)$  ng/ml (N:< 0.5) in NIFRG. Median neutrophil-to-lymphocyte ratio (NLR) was  $8.00(3.00-15.00)$  in the IRFG, whereas it was  $5.00(3.00-9)$  in the NIFRG ( $p = 0.001$ ). Median platelet-to-lymphocyte ratio (PLR) was  $21.00(9.00-41.00)$  in the IRFG, whereas it was  $16.00(7.25-27.75)$  in the NIFRG and was not significant ( $p = 0.001$ ) (Table 2).

The distribution of hospitalization clinic was shown in table-1. The classification of diagnosis was extensively evaluated. Patients diagnosed with anemia and gastrointestinal bleeding were significantly higher in NIFRG ( $p < 0.05$ ). However, patients suffering from gastroenteritis, cellulitis, cholangitis, abscess, upper respiratory tract infection, sepsis, urinary tract infection, central venous catheter infection, diabetes mellitus and pneumonia were significantly higher in IRFG ( $p < 0.05$ , Table 1).

Red blood distribution width, monocytes (%), lymphocytes (%), basophils (%), albumin, iron, and folate levels significantly elevated in NIFRG compared to IRFG. Among laboratory parameters of IRFG, WBC, MCV, Hgb, neutrophil count, creatinine, CRP, PCT, and ESR levels were significantly higher than that of NIFRG. Other laboratory parameters were comparable in both groups (Table 2).

The time to initiate the first antibiotic was  $2.12 \pm 1.98$  days in IRFG and  $2.70 \pm 2.78$  days in NIFRG ( $p = 0.021$ ). The duration of first antibiotic usage was  $4.54 \pm 3.08$  and  $5.35 \pm 3.8$  days in IRFG and NIFRG, respectively, and there was a statistically significant difference between groups ( $p = 0.023$ ). Average number of antibiotics administered was  $1.77 \pm 0.99$  in IRFG patients and  $1.47 \pm 0.77$  in NIFRG patients, along with a significant difference between the

groups ( $p = 0.001$ ) (Table 3). The first empirical antibiotic was ceftriaxone, which was used by 82 (40.1%) IRFG patients and 120 (32.1%) NIFRG patients ( $p = 0.024$ ). Secondly, moxifloxacin was administered to 36 (17.7%) IRFG patients and 42 (11.2%) NIFRG patients ( $p = 0.001$ ). The final antibiotic was ampicillin- sulbactam and it was used by 17 (8.4%) and 34 (9.1%) patients of IRFG and NIFRG, respectively ( $p = 0.155$ ).

**Table 1.** Demographic data and diagnostic distribution of patients in non-infectious fever and infectious fever groups

Features	Non-infectious Fever Group (n:374)	Infectious Fever Group (n:203)	P
Age	65.41±18.03	66.42 ±16.58	0.509
Gender(male)	206 (55.1)	133 (65.5)	<b>0.015</b>
Thyroid disease	119 (31.8)	63 (31.0)	0.847
Gastroenteritis	0	8 (3.9)	<b>0.001</b>
Cellulitis	0	4 (2.0)	<b>0.006</b>
Cholangitis	0	10 (5.0)	<b>0.001</b>
Abscess	0	3 (1.5)	<b>0.018</b>
URTD	0	6 (3.0)	<b>0.001</b>
Sepsis	0	4 (2.0)	<b>0.006</b>
USI	1 (0.3)	35 (17.2)	<b>0.001</b>
CRI	2 (0.5)	9 (4.4)	<b>0.001</b>
DM	128 (34.2)	92 (45.3)	<b>0.009</b>
Anemia	71 (19.0)	16 (7.9)	<b>0.001</b>

Abbreviations: COPD; Chronic obstructive pulmonary disease, FMF; Familial Mediterranean Fever, CCHF; Crimean-Congo hemorrhagic fever, ITP; Immune thrombocytopenic purpura, URTD; Upper respiratory tract diseases, USI; Urinary systems infectious, IBD; Inflammatory bowel disease, CRI; catheter-related infection, CVD; Cerebrovascular disease, DM; Diabetes Mellitus, CRF; Chronic renal failure, CHF; Congestive heart failure, GI; Gastrointestinal, HM; Hematologic malignancy, DCA; Diabetic ketoacidosis

Parameters	Non-infectious Fever Group (n:374)	Infectious Fever Group (n:203)	P
White blood cell count, 10 <sup>3</sup> /mm <sup>3</sup>	10.30±8.83	12.30±10.20	<b>0.014</b>
Platelet count, 10 <sup>3</sup> /mm <sup>3</sup>	232.26±123.96	231.71±150.80	0.963
Neutrophil count, 10 <sup>3</sup> /mm <sup>3</sup>	7.94±7.07	9.65±6.40	<b>0.004</b>
MCV	85.37±13.74	88.38±7.84	<b>0.004</b>
Lymphocyte count, 10 <sup>3</sup> /mm <sup>3</sup>	1.58±3.04	1.73±8.13	0.743
Hemoglobin, g/dl	9.63±2.66	10.17±2.36	<b>0.017</b>
Hematocrit, %	29.22±7.97	30.48±7.40	0.064
Albumin, gr/L	3.06±0.65	2.91±0.60	<b>0.006</b>
ALT, IU/L	19.00 [11.00-39.00]	16.50 [10.00-38.00]	0.195
AST, IU/L	71.16±270.44	54.13±113.7	0.394
C-reactive protein (CRP), mg/L	97.49±88.77	141.82±107.19	<b>0.001</b>
Sedimentation, mm/h	62.68±39.29	71.47±34.28	<b>0.013</b>
LDH, U/L	460.80±876.02	334.76±413.0	0.094
Procalcitonin, ng/mL	0.36 [0.09-1.11]	1.03 [0.22-8.41]	<b>0.001</b>
NLR	5 [3.00-9]	8 [3.00-15.00]	<b>0.001</b>
PLR	21.00 (9.00-41.00)	16.00 (7.25-27.75)	<b>0.001</b>
TSH	0,93 [0.45-1.69]	0.77 [0.35-1.48]	0.139

Abbreviations: MCV; Mean corpuscular volume, Alb; Albumine, ALT; Alanine aminotransferase, AST; aspartat aminotransferaz, CRP; C-reactive protein, LDH; Lactate dehydrogenase, ESR; Erythrocyte Sedimentation Rate, TSH; Thyroid-stimulating hormone, NLR; Neutrophil/Lymphocyte

Parameters	Non-infectious Fever Group (n:374)	Infectious Fever Group (n:203)	P
First Antibiotic Start Time (Day)	2.70±2.78	2.12±1.98	0.021
First Antibiotic Usage Time (Day)	5.35±3.8	4.54±3.08	0.023
Mean antibiotic count	1.47±0.77	1.77±0.99	0.001
<b>Frequently Used Antibiotics Respectively</b>			
Seftriakson	120 (%32.1)	82 (%40.1)	0.024
Moksifloksasin	42 (%11.2)	36 (%17.7)	0.001
Ampisilin/Sulbaktam	34 (%9.1)	17 (%8.4)	0.155
Piperasilin-Tazobaktam	14 (%3.7)	9(%4.4)	0.094

## DISCUSSION

In this study, it was observed that the time to start empirical antibiotics was delayed in NIRFG compared to IRFG. In addition, we observed that the number of antibiotics used in IRFG patients was significantly higher than that of NIRFG. The duration of empirical antibiotic usage was significantly longer in NIRFG with respect to IRFG. The reason behind this might be the fact that fever in NIRFG patients did not alleviate in spite of the antibiotics and the inflammatory markers did not improve. The most commonly used antibiotic was ceftriaxone since broad-spectrum antibiotics are prescribed with the approval of an infection disease specialist, and additionally third generation cephalosporins are widely preferred in prescriptions in accordance with legal regulations of our country. Quinolones were the second most commonly used antibiotics since they are accessible and their administration in oral form is relatively easy. Several studies have emphasized that shorter treatments ought to be applied considering the potential side effects, antibiotic resistant organisms, and increased costs.<sup>11-13</sup>

WBC is an indicator, which is actively used in fever identification. WBC levels elevate in IRFG, whereas they are low in NIRFG. CRP is another crucial indicator for the inflammatory response of the body. The proportion of patients with low hemoglobin and low serum albumin was higher in IRFG, while it was lower in NIRFG. In our study, we demonstrated that NIRFG patients represented significantly lower WBC, CRP, ESR, PCT, Hgb, MCV, neutrophil levels. This may be due to chronic anemia, which is a common consequence of hepcidin and cytokines such as TNF-alpha, IL1, IL6.<sup>14,15</sup> Additionally, lower albumin levels in IRFG may occur due to the negative phase reactant in infectious diseases.<sup>16</sup> Many randomized controlled trials have investigated the PCT levels to assist decisions regarding the administration of antibiotic therapy.<sup>17</sup> In one study, PCT and CRP levels significantly increased in cancer patients with infection compared to those who didn't have infection and significantly elevated in all gastric can-

cer groups with respect to the control group. CRP and PCT are two important markers for the diagnosis of infection in cancer patients.<sup>18</sup> In another study, infected inactive SLE had a significantly higher CRP level than uninfected inactive SLE.<sup>19</sup>

In a study by Are Naess et al., it was shown that NLR was higher in patients hospitalized due to fever due to bacterial infection compared to those due to noninfectious causes.<sup>20</sup> Similarly, in our study, NLR was found higher in IRFG, but lower in NIRFG. However, there was no significant difference in PLR. Pneumonia, catheter-related infection (CRI), Urinary system infections (USI), Upper respiratory tract diseases (URTD), abscess, cholangitis, cellulitis, gastroenteritis are commonly observed in IRFG since all of those diseases are infection related. It is common for diseases such as GI bleeding, anemia, diabetes, etc. to be significantly higher in the NIRFG. In community-acquired pneumonia, empirical antimicrobial therapy was applied to patients whose microbiological results have not yet been concluded. Guidelines suggest that empirical antibiotic treatment selection includes streptococci pneumonia and atypical pathogens.<sup>21,22</sup> In several studies, no significant difference was observed between the use of macrolides, beta lactam antibiotics and fluoroquinolones in the antibiotic regimen in CAP patients.<sup>23</sup> In our study, moxifloxacin antibiotics that belong to fluoroquinolone are detected to be widely used in pneumonia.

Our study has two important limiting factors, as the first being a retrospective study, and the second being a single-center study. Excluding other fever-related diseases might be another limitation of our study. However, our study makes significant contributions to the empirical antibiotic treatment of infection and non-infection related fever diseases.

Infections affect all organs and systems. People with diabetes often suffer from conditions including feet infections, malignant external otitis, rhinocerebral mucormycosis,

and gangrenous cholecystitis. Infection process, in addition to increased morbidity, may be among the initial indicators of diabetes or may trigger factors for disease-specific complications such as diabetic ketoacidosis and hypoglycemia.<sup>24</sup> Co-occurrence of fever and GI bleeding may suggest the presence of a concomitant infection disease.

As a result of this study, empirical antibiotic treatment management should be taken into consideration in comorbid diseases such as T2DM, thyroid diseases, chronic kidney disease (CKD), non-hematological malignancies(NHM), pneumonia, urinary tract infection (UTI) accompanied by fever. In patients with diabetes mellitus, fever is a common comorbidity factor in both infectious and non-infectious conditions. The most commonly observed comorbid infections are diabetes mellitus and CKD. Thus, additional consideration is required to control infection in those patients. The anamnesis of the patients should be taken carefully and the laboratory examinations should be evaluated clearly.

## CONCLUSION

Clinicians are required to avoid using wide-spectrum antibiotic selection and exposing the patients to excessive antibiotics until the culture results are revealed. Some of the hemogram parameters such as NLR and PLR are easy, fast and inexpensive to use as a marker of patient outcome, can be useful in daily clinical practice and empirical antibiotic use in developing countries.

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**Ethics approval for this study was obtained from Sakarya University Faculty of Medicine Non-Interventional Ethics Committee (Number: 71522473 / 050.01.04/47).**



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